



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : BORODY *et al.*

Art Unit : 1616

Serial No. : 10/506,728

Examiner : Holt, Andriae M.

Filed : June 27, 2005

Confirm. No.: 7029

Title : ELECTROLYTE PURGATIVE

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Sir:

I, **Thomas J. Borody**, declare as follows,

1) I am an inventor of the above-captioned application, which is the National Stage of International Application. No. PCT/AU03/00257, filed March 4, 2003, which claims benefit of priority to Australian provisional patent application Serial No. PS 0887, filed March 4, 2002. I am the same Thomas J. Borody who made a Declaration, dated 11 June 2009, in respect of the above-captioned application.

2) As advised in my previous Declaration, I am a Gastroenterologist. I obtained my BSc and MBBS from the University of New South Wales. I obtained my Ph.D. in medicine from the University of Newcastle and my M.D. from the University of New South Wales. I have been a Fellow of the Royal Australasian College of Physicians since 1982. I have been a Fellow of the American College of Gastroenterology since 1993 and a Fellow of the American College of Physicians (Philadelphia, PA) since 2002. I was a Clinical Fellow in Gastroenterology at the Mayo Clinic in Rochester, Minnesota. I am the Founder and have been the Medical Director for the Centre for Digestive Diseases in New South Wales since 1985 and have been a Consulting Gastroenterologist to the Sydney Adventist Hospital since 1995.

3) I have published more than 120 scientific articles. I am a reviewer for the Medical Journal of Australia, the American Journal of Gastroenterology, Digestive Diseases and Sciences and the Journal of Gastroenterology and Hepatology. I am an inventor on 18 issued US patents.

4) I have reviewed the Office Action, mailed September 14, 2009, in connection with the above-captioned application.

5) The above-captioned application provides compositions that can be used for orthostatic lavage to clean the bowel of fecal matter, as a simple purgative or in electrolyte

replacement therapy. The pending claims recite compositions for use in a purgative and methods of inducing purgation of the colon of a patient.

6) The Office Action cites the combination of Kawakami (JP 05306221) and Colliopoulos (U.S. Pat. No. 5,232,699) and Cockerill (U.S. Pat. No. 4,452,779) in the rejection of certain of the claims. I am familiar with and have reviewed these documents.

7) Kawakami is a 1993 document and describes a composition that is an isotonic magnesium citrate solution that includes sodium chloride, potassium hydroxide and a degradable sugar such as sucrose. Kawakami describes using an amount of degradable sugar to provide an isosmolar (290-310 mOsm/L) liquid. The composition claimed in the above-captioned application is hyperosmolar in-part created by the use of minimally degradable sugars to enhance the faecuresis, whereas Kawakami does not mention anything regarding a hyperosmolar liquid nor the active use of sugars to promote faecuresis. Indeed, he describes the use of the sugars to adjust osmolarity so as to prevent hyperosmolarity.

The magnesium citrate-based composition of Kawakami is similar in composition to a commercially available purgative known as PicoPrep™ purgative. PicoPrep™ purgative is a magnesium citrate based bowel cleansing composition that includes the stool softener sodium picosulfate. The Kawakami composition differs from the PicoPrep™ purgative in that Kawakami includes an easily digestible sugar and does not include sodium picosulfate, which is an optional stool softener. PicoPrep™ purgative also is a more hypertonic solution than the composition of Kawakami. The composition of Kawakami is administered as a 900 mL aqueous solution, while the PicoPrep™ purgative is administered as a 250 mL solution and water is administered in the time following administration of PicoPrep™ purgative.

Administration of PicoPrep™ purgative with fruit juice, although not recommended, closely reproduces the Kawakami preparation, since the juice provides the degradable sugar present in the formulation of Kawakami (see, *e.g.*, Duthie, *NutriDate* Vol. 18, Number 1 (2007), page 8). For example, when the PicoPrep™ purgative is prepared using apple juice, the purgative includes some of the same degradable sugars taught in Kawakami, such as sucrose and fructose.

Colliopoulos describes laxatives containing psyllium and sennoside dispersed in a food grade fat and a sweetening agent. Laxative compositions containing senna or sennosides are known to have undesirable side effects, such as pain, bloating and cramping.

The compositions as claimed in the instant application avoid these side effects, particularly by using a minimally degradable sugar(s) and excluding senna or sennosides. The minimally degradable sugar(s) in the purgative compositions described and claimed in the above-captioned patent application are present at a level that has a laxative effect. Sucrose is a degradable sugar readily absorbed by the GI tract and generally does not have a laxative effect when eaten in excess. Xylose is partially absorbed by the GI tract and is resistant to endogenous digestion in the gastrointestinal tract. Xylose does have a laxative effect when ingested in excess.

8) The compositions of the instant claims can be used in a purgative, such as a hypertonic purgative. As described in the specification, a purgative including the instant composition, which includes a synergistic combination of water-soluble sodium, potassium and magnesium and minimally degradable sugar(s), is more effective as a bowel cleansing preparation than existing purgative agents. The water-soluble sodium, potassium and magnesium salts and the xylose or other minimally degradable sugar such as mannitol or inulin in the instant compositions are used to increase the tonicity of the active solution. When prepared as a hypertonic solution, a reduced volume of the composition can be consumed, resulting in better tolerability and reduction in adverse side effects, thereby improving patient compliance. The use of minimally degradable sugars in the instant composition instead of an easily degradable sugar avoids the gas formation, bloating and cramps that can be caused by degradable sugars, such as sucrose, used in commercial products and described in the compositions of Kawakami and Colliopoulos. The minimally degradable sugars used in the claimed compositions help to induce diarrhea and thus accelerate bowel cleansing. The salts in the instant composition reduce the electrolyte loss during bowel purgation. In the instant compositions, palatable salts such as gluconate, citrate and aspartate can be used to improve palatability since these salts are known to locally reduce stimulation of salt receptors found on the tongue.

9) Furthermore, compositions within the scope of the claims of the above-captioned patent application have properties that differ from the composition described in Kawakami. Clinical studies were conducted under my instruction in which a presently available PicoPrepTM composition was compared with a composition made in accordance with the description of the above-captioned application and within the scope of the instant claims. For

the purposes of this Declaration, the composition within the scope of the instant claims that was tested in the clinical studies will be referred to as "Hydroprep."

The PicoPrep™ composition was provided in the form of 3 sachets (3 sachets per sachet box and representing a single treatment), each sachet containing 10 mg sodium picosulphate, 3.5 g magnesium oxide (heavy), 12.0 g citric acid (anhydrous) and 36 mg of aspartame. The sachets were dissolved in water, the magnesium oxide and citric acid components forming magnesium citrate, an osmotic purgative. In this regard, PicoPrep™ generally is administered as a 250 mL aqueous solution, followed by the administration of several glasses of water over the course of several hours. The three sachets were mixed with the water prior to administration giving a total of 30 mg sodium picosulphate, 10.5 g magnesium oxide (heavy), 36 g of citric acid (anhydrous) and 108 mg of aspartame.

Although advised not to do so, some patients have reported taking PicoPrep™ formulations with fruit juices of various kinds, such as apple juice, or with cordials. When taken in this manner, the resulting PicoPrep™ formulation is very similar to the composition of Kawakami because of the degradable sugar present in the apple juice or cordials.

The Hydroprep composition was made as described in the above-captioned application and contained in total 30 mg of sodium picosulphate, 8 g of magnesium sulphate, 4.5 g of sodium sulphate, 3.5 g of potassium gluconate, 3.5 g of sodium chloride and 8 g of mannitol provided in the form of 30 capsules, which were administered together with water as a single treatment.

10) It is important to note that mannitol is a minimally degradable sugar. Mannitol is not metabolized to any appreciable extent and is minimally reabsorbed in the body (see, *e.g.*, *Remington Pharmaceutical Sciences* (16th edition, Osol, ed., 1980), page 873).

11) On administration of the PicoPrep™ composition to 14 patients, administration of the PicoPrep™ composition with a degradable sugar such as sucrose to 7 patients, and administration of the Hydroprep composition to 26 patients, it was found that there was accelerated and significantly better bowel wall cleansing in patients using the Hydroprep composition as compared with the PicoPrep™ compositions, even in those patients with constipation (which usually results in much residual faeces). Four of the patients refused treatment with the standard liquid PicoPrep™ composition because of prior experience with vomiting. These same patients had no problems with the use of the Hydroprep composition.

12) Notable acceleration with respect to time to first bowel evacuation was observed with the Hydroprep composition as compared to the PicoPrepTM compositions. First defecation in patients administered the Hydroprep composition occurred between 2 and 4 hours after administration of the Hydroprep composition. In comparison, first defecation in patients administered the PicoPrepTM composition, prepared using water as directed or prepared using a juice or beverage containing a degradable sugar, such as apple juice, occurred between 3 and 5 hours after administration. Accordingly, a more rapid onset of cleansing was observed with the Hydroprep composition as compared to the PicoPrepTM composition and a composition similar to that described in Kawakami.

13) Notable reduction in the reported occurrence of adverse side effects also was observed with the Hydroprep composition as compared to the PicoPrepTM compositions. It was found that patients administered the Hydroprep composition experienced a reduction in side effects, including a 92% reduction in nausea, no vomiting and a 37% reduction in headaches as compared to the patients administered the PicoPrepTM compositions.

14) Significant improvement in bowel wall cleansing was observed in patients administered the Hydroprep composition as compared to the PicoPrepTM compositions. The bowel wall cleansing was judged blindly by two observers and documented by photography. The PicoPrepTM composition had rating scores of 6 to 7 as evidenced in Table 1.

Table 1. PicoPrepTM rating scores.

Patient	Rating Score – Bowel wall cleansing with PicoPrep TM
Patient 1	6.2
Patient 2	6.0
Patient 3	6.3
Patient 4	6.1
Patient 5	6.0
Patient 6	6.4
Patient 7	6.7
Patient 8	6.6
Patient 9	6.5
Patient 10	6.1
Patient 11	6.4
Patient 12	6.1

Patient 13	6.2
Patient 14	6.0

The mean rating score was 6.25 out of 10. Similar ratings were found even when the standard PicoPrepTM picosulphate content was doubled. There was no increase in cleansing power when the picosulphate content of the composition was doubled.

In comparison, the Hydroprep composition resulted in a consistently cleaner bowel wall and had a rating score of 8.2 to 9.5 as evidenced by the data in Table 2:

Table 2. Hydroprep composition rating scores.

Patient	Rating Score – Bowel wall cleansing with Hydroprep
Patient 1	8.3
Patient 2	8.6
Patient 3	8.9
Patient 4	9.0
Patient 5	9.1
Patient 6	9.3
Patient 7	9.4
Patient 8	8.5
Patient 9	8.7
Patient 10	8.0
Patient 11	8.2
Patient 12	8.4
Patient 13	8.7
Patient 14	8.3
Patient 15	9.2
Patient 16	8.7
Patient 17	8.9
Patient 18	9.0
Patient 19	9.1
Patient 20	9.4
Patient 21	9.5
Patient 22	8.7
Patient 23	9.2
Patient 24	9.1
Patient 25	9.0

Patient 26	8.7
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The mean rating score was 8.84 out of 10, which had a standard deviation P of less than 0.04.

15) The bowel wall cleansing results using the Hydroprep composition, which includes the combination of water-soluble sodium, potassium and magnesium salts and minimally degradable sugar(s) in the composition as claimed in the above-captioned application, are significantly different from the results using the PicoPrep™ compositions. As stated above, when the standard PicoPrep™ composition was doubled (with a doubling of the picosulphate concentration), the composition did not show any increased cleansing power as would have been expected. In comparison, the Hydroprep composition showed significantly improved bowel cleansing and the results indicate that there is synergism occurring between the components of the composition. The improved bowel cleansing results were unexpected, as various combinations of ratios of salts and sugars were tested with increased picosulphate concentration and concentrations of the other salts, but it was only when formulations falling within the scope of the claims of the above-captioned application were used that there was such a dramatic improvement in bowel cleansing.

16) Attached are various photographs showing the results of the bowel cleaning. Figures 1-11 are photographs of bowels of patients to whom the Hydroprep composition was administered. Figures 12-19 are photographs of bowels of patients to whom the standard aqueous PicoPrep™ composition was administered. Figures 20-28 are photographs of bowels of patients that took PicoPrep™ composition prepared in a fruit juice or other beverage containing a degradable sugar. The photographs of Figures 1-11 clearly show the cleansing superiority of the Hydroprep composition over the PicoPrep™ compositions.

17) All patients treated with the Hydroprep composition who had previously experienced treatment with the standard PicoPrep™ composition preferred the Hydroprep composition over the PicoPrep™ compositions.

18) The combination of the water soluble sodium, potassium and magnesium salts and minimally degradable sugar(s) in the Hydroprep composition result in a product that is superior to the presently available PicoPrep™ composition with marked improvement in bowel cleansing even in constipated patients. The superior cleansing was achieved by use of a small number of capsules containing the Hydroprep composition and in less time than with

PicoPrepTM composition. Side effects such as vomiting, nausea and headaches were significantly reduced in patients administered the Hydroprep composition.

19) Similar synergism to that referred to above was found with Hydroprep compositions in which the minimally degradable sugar mannitol was replaced with xylose or inulin. Inulin is composed of fructose units joined by a $\beta(2\rightarrow1)$ glycosidic bond and is a minimally degradable sugar, passing through the upper colon unchanged. In the last 78 patients treated with a Hydroprep composition in which the mannitol was replaced with xylose, an increased synergism was observed to the extent that instead of using 30 capsules to obtain equivalent cleansing observed with the Hydroprep composition containing mannitol, only 18 capsules of Hydroprep composition containing xylose needed to be used.

20) Because the composition described in Kawakami is a magnesium citrate-based purgative similar to PicoPrepTM, and formulations that include the composition claimed in the instant application were found to be more effective at cleansing the bowel than a magnesium citrate-based purgative like PicoPrepTM, it can be inferred that formulations that include the composition claimed in the instant application are more effective at cleansing the bowel than the magnesium citrate-based purgative described in Kawakami.

21) As noted above, some patients have reported taking PicoPrepTM formulations with fruit juices of various kinds, such as apple juice, or cordials. When taken in this manner, the PicoPrepTM formulation would be very similar to the composition of Kawakami, which is a magnesium citrate based purgative with added degradable sugars. The only difference is that the PicoPrepTM formulation includes a stool softener. As mentioned above, doubling of the stool softener did not improve the bowel cleaning ability of the PicoPrepTM formulations. Thus, one would conclude that the addition of a stool softener to the composition of Kawakami would have little effect on its bowel cleaning ability. In patients that reported taking the PicoPrepTM formulation prepared with a liquid containing a degradable sugar, there is no enhancement of cleansing as observed with the Hydroprep compositions that include the minimally degradable sugar and within the scope of the above-captioned patent application. In patients that took the PicoPrepTM formulations with fruit juice or cordials, it is observed that the right colon remains covered with a fine faecal coating. Thus, compositions similar to the composition of Kawakami, containing a magnesium citrate purgative with a degradable

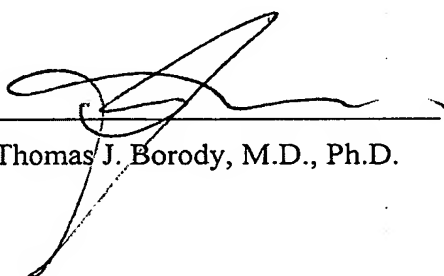
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sugar present, give different results from those obtained with the compositions within the scope of the claims of the above-captioned application.

22) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

9th March 2010
Date


Thomas J. Borody, M.D., Ph.D.

FIGURES ACCOMPANYING DECLARATION PURSUANT TO 37 C.F.R. §1.132

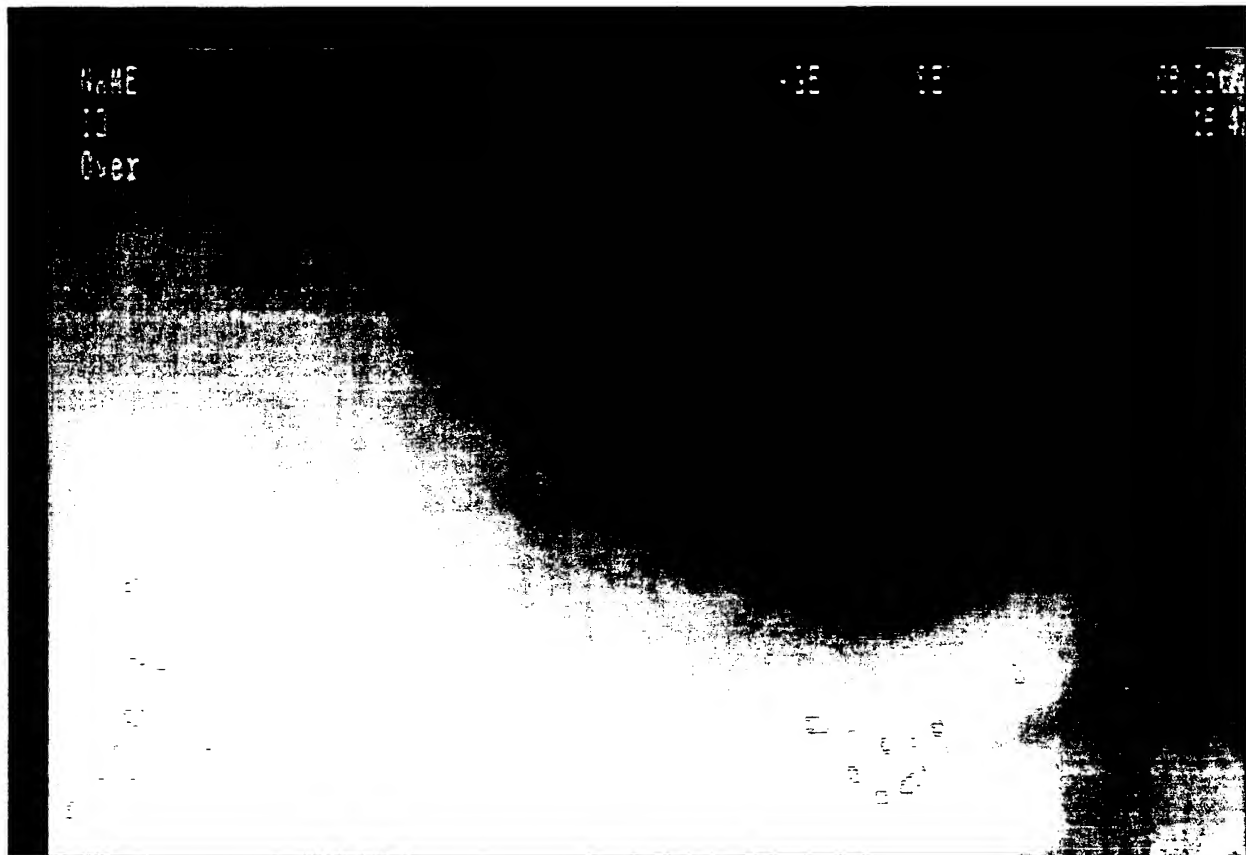


Figure 1. Photograph of bowel of patient administered Hydroprep composition.

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Figure 2. Photograph of bowel of patient administered Hydroprep composition.

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Figure 3. Photograph of bowel of patient administered Hydroprep composition.

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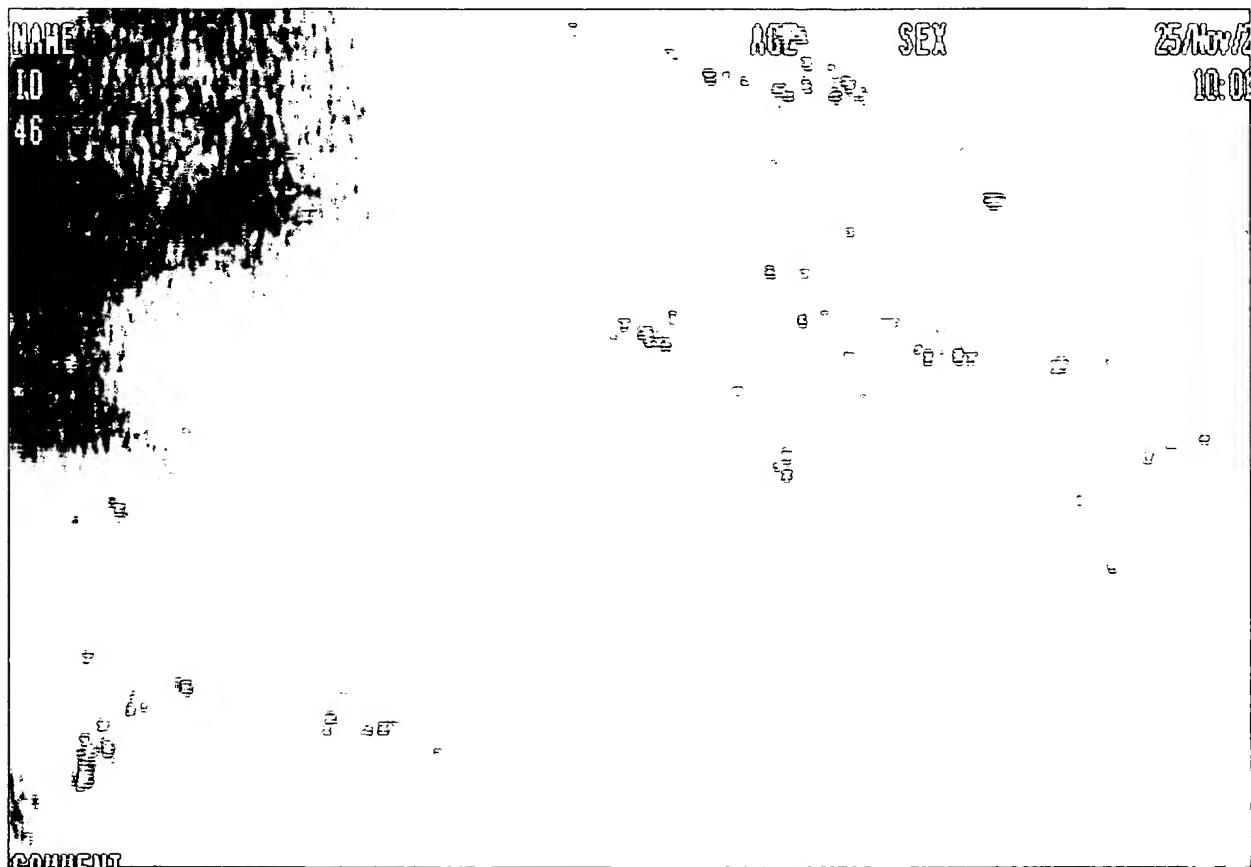


Figure 4. Photograph of bowel of patient administered Hydroprep composition.

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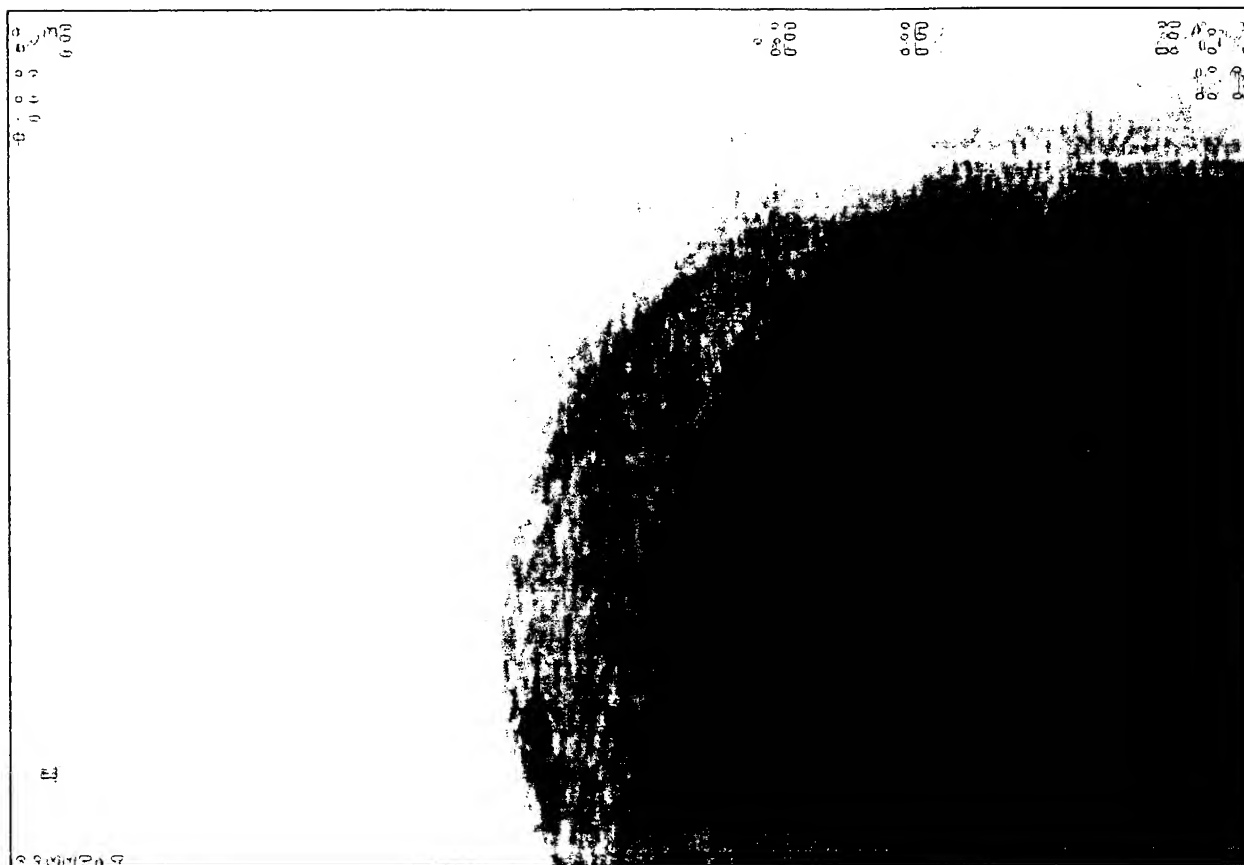


Figure 5. Photograph of bowel of patient administered Hydroprep composition.

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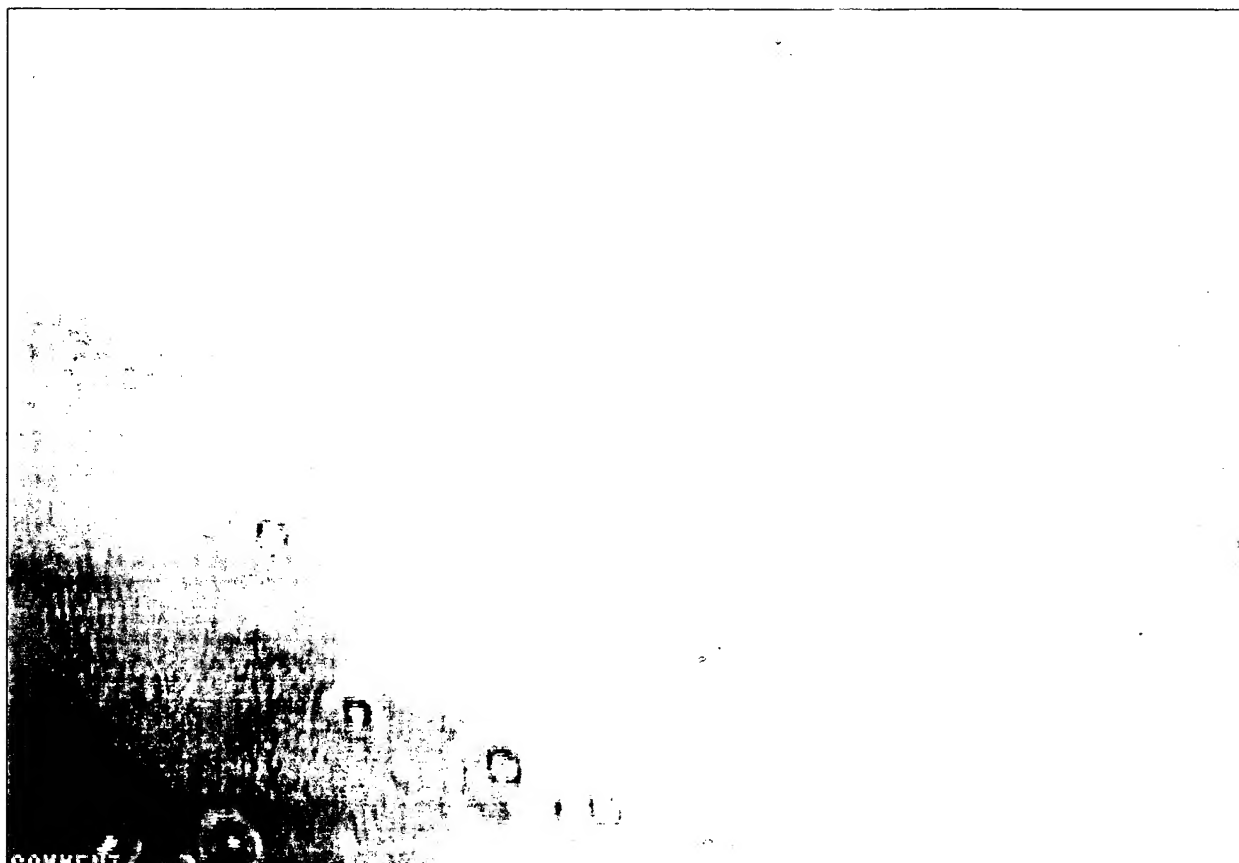


Figure 6. Photograph of bowel of patient administered Hydroprep composition.

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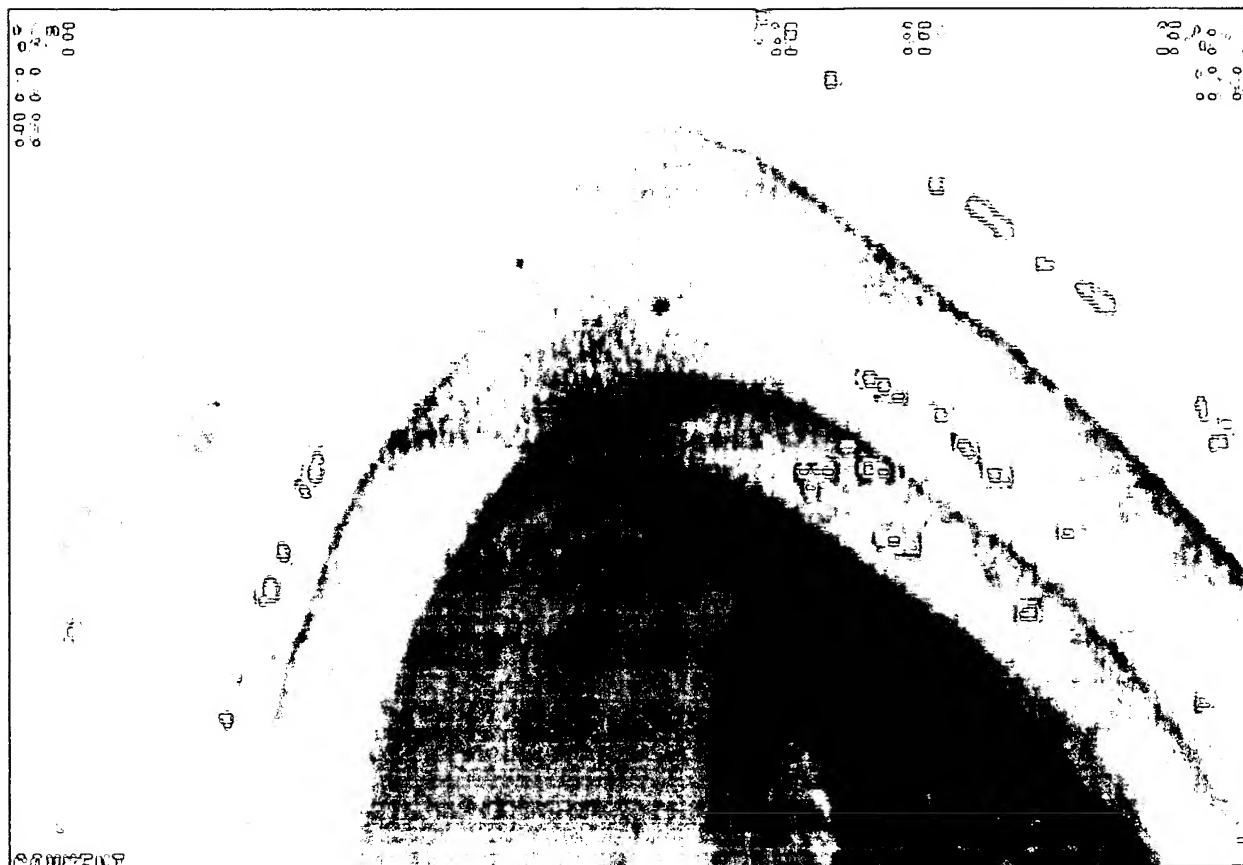


Figure 7. Photograph of bowel of patient administered Hydroprep composition.

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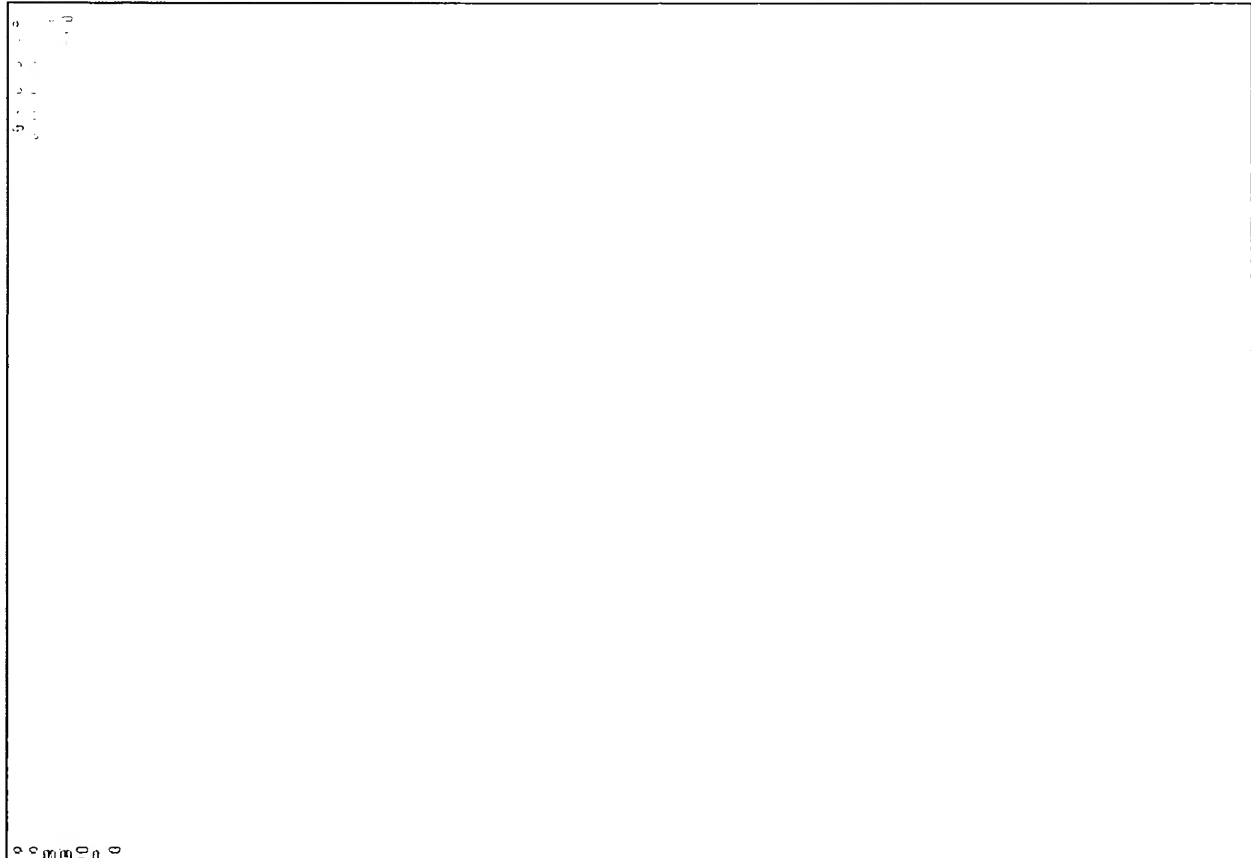


Figure 8. Photograph of bowel of patient administered Hydroprep composition.

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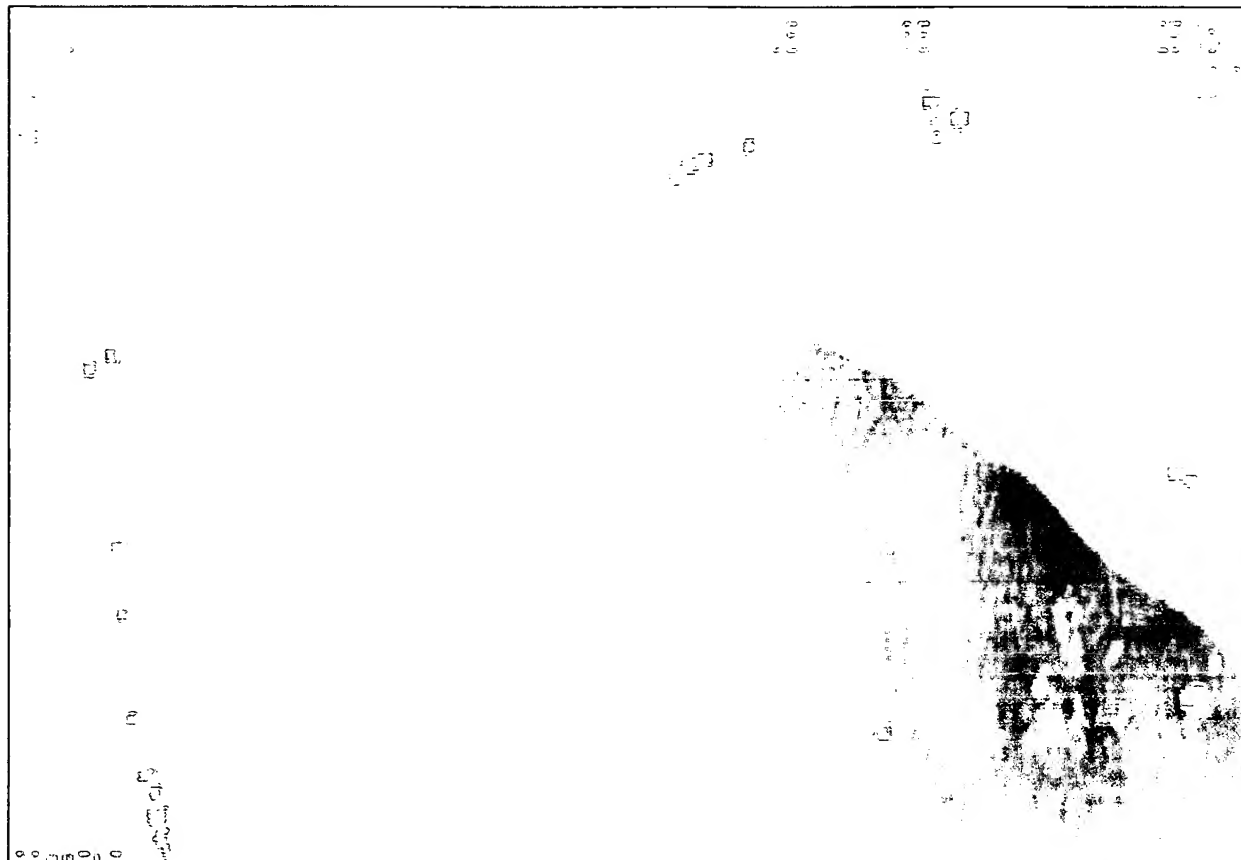


Figure 9. Photograph of bowel of patient administered Hydroprep composition.

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Figure 10. Photograph of bowel of patient administered Hydroprep composition.

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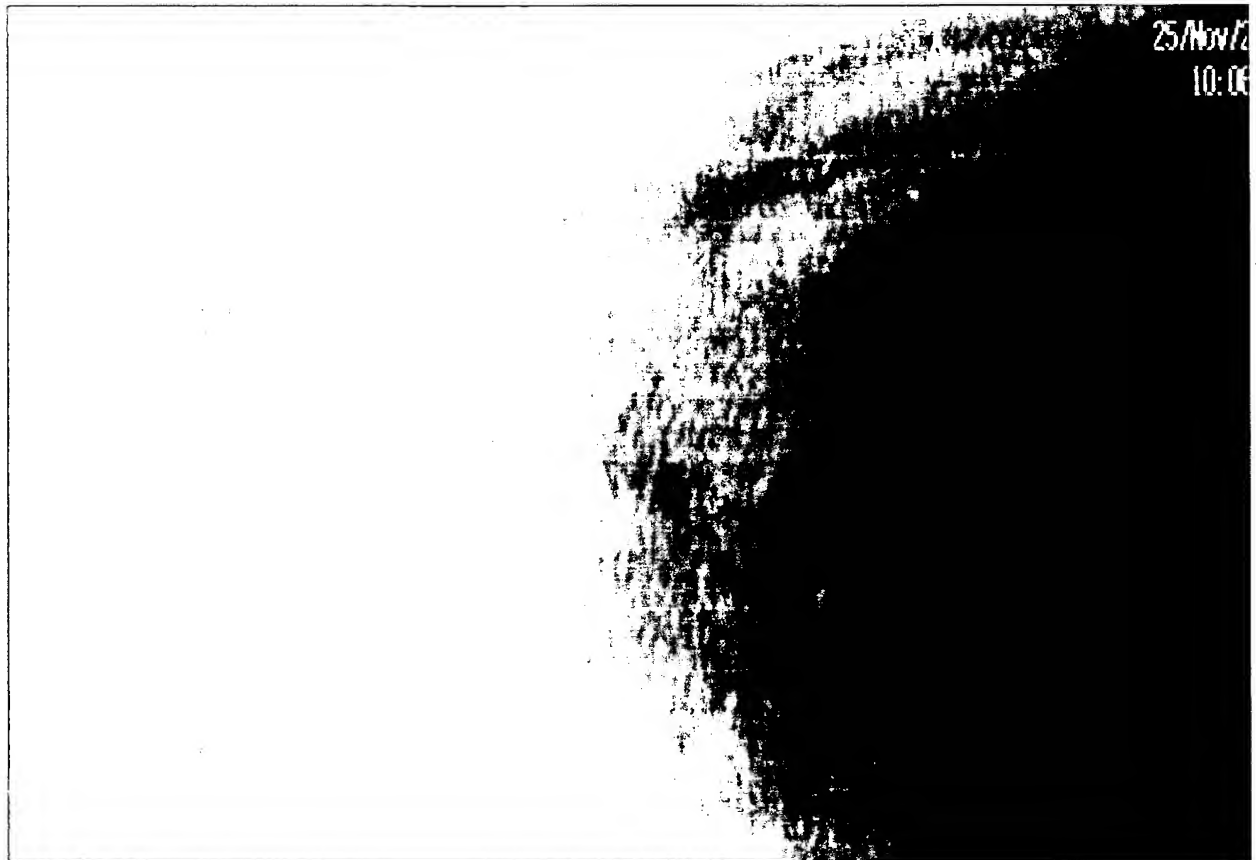


Figure 11. Photograph of bowel of patient administered Hydroprep composition.

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Figure 12. Photograph of bowel of patient administered PicoPrep™ composition.

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Figure 13. Photograph of bowel of patient administered PicoPrep™ composition.

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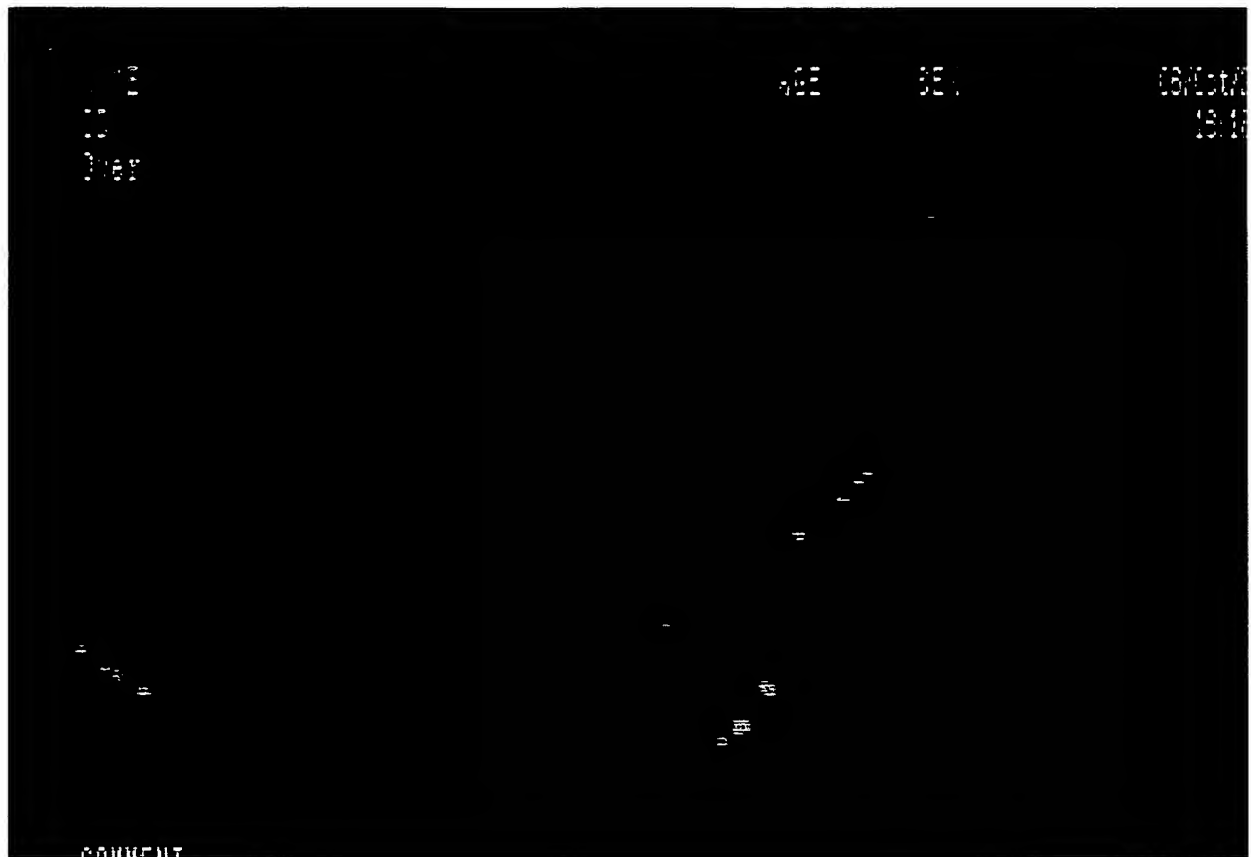


Figure 14. Photograph of bowel of patient administered PicoPrep™ composition.

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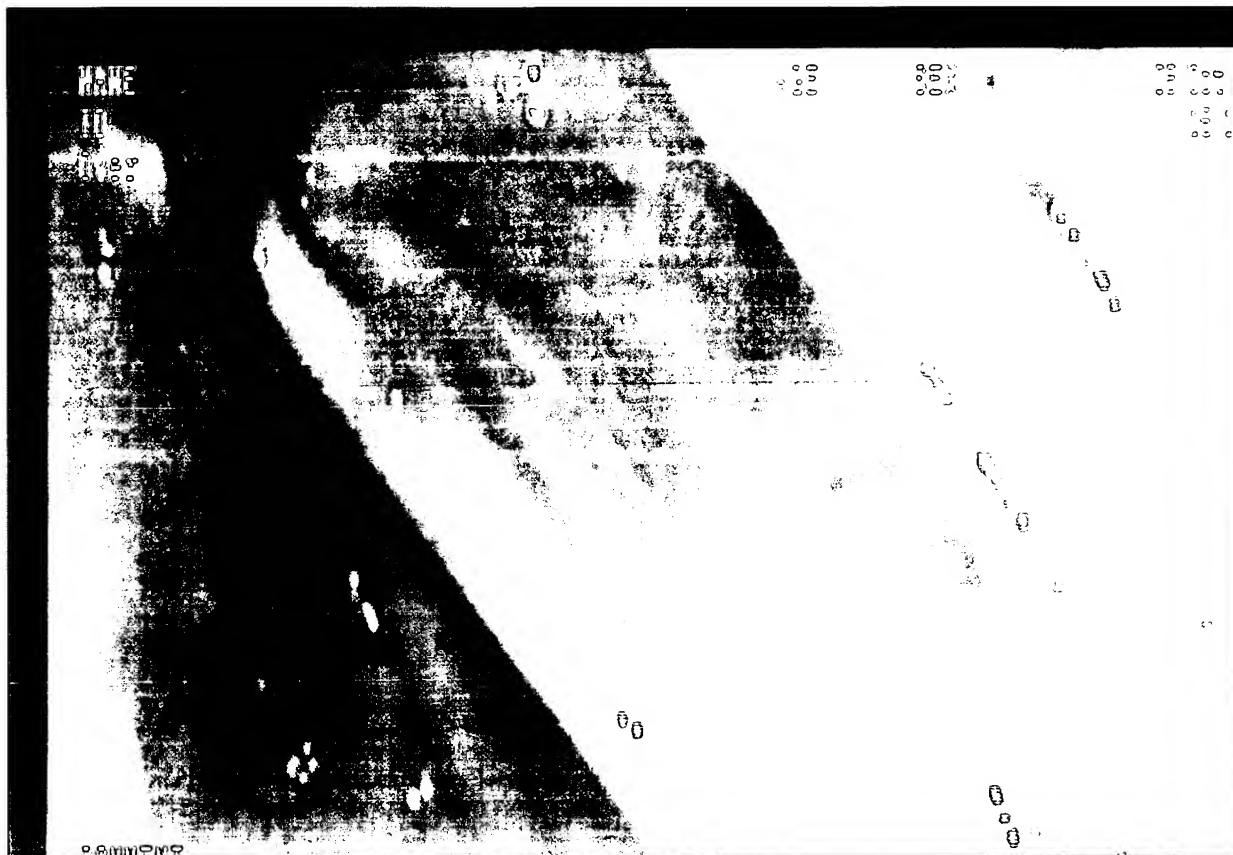


Figure 15. Photograph of bowel of patient administered PicoPrepTM composition.

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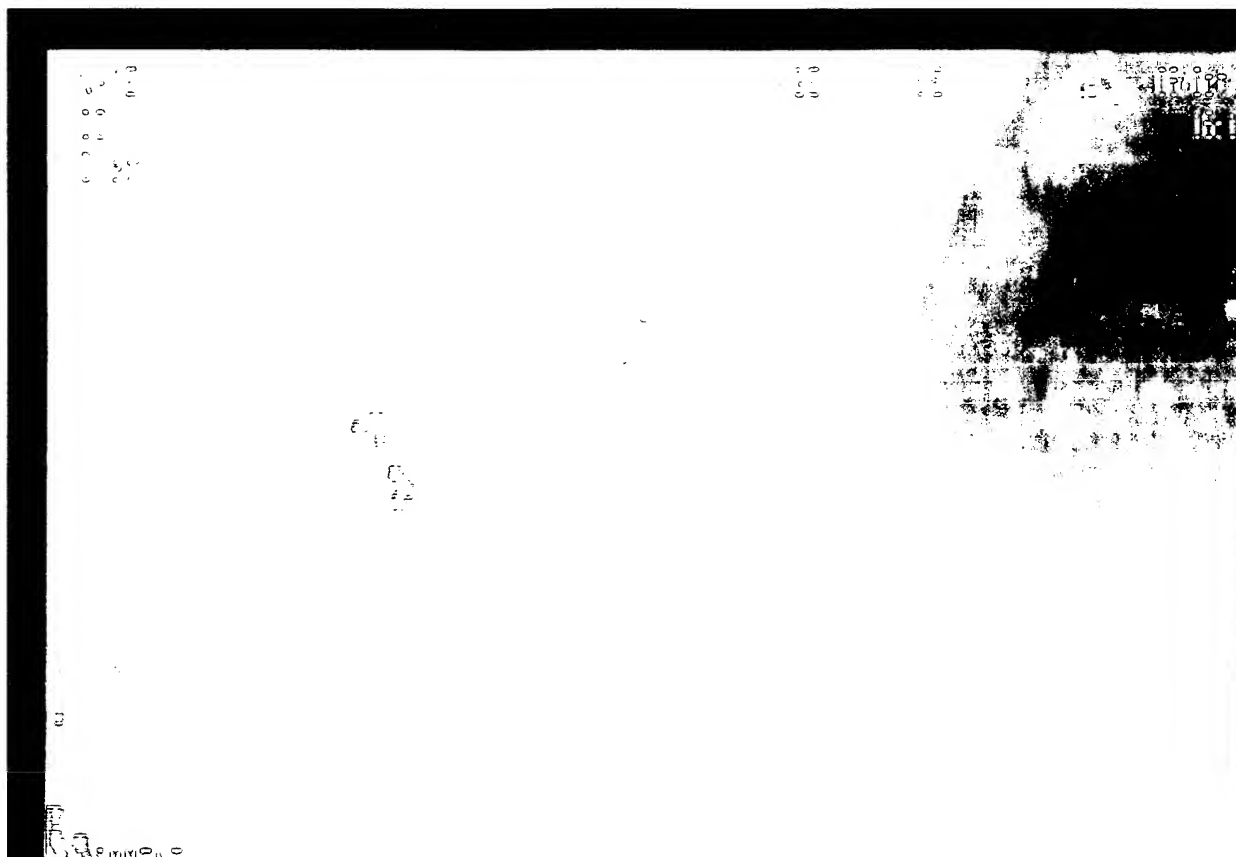


Figure 16. Photograph of bowel of patient administered PicoPrepTM composition.

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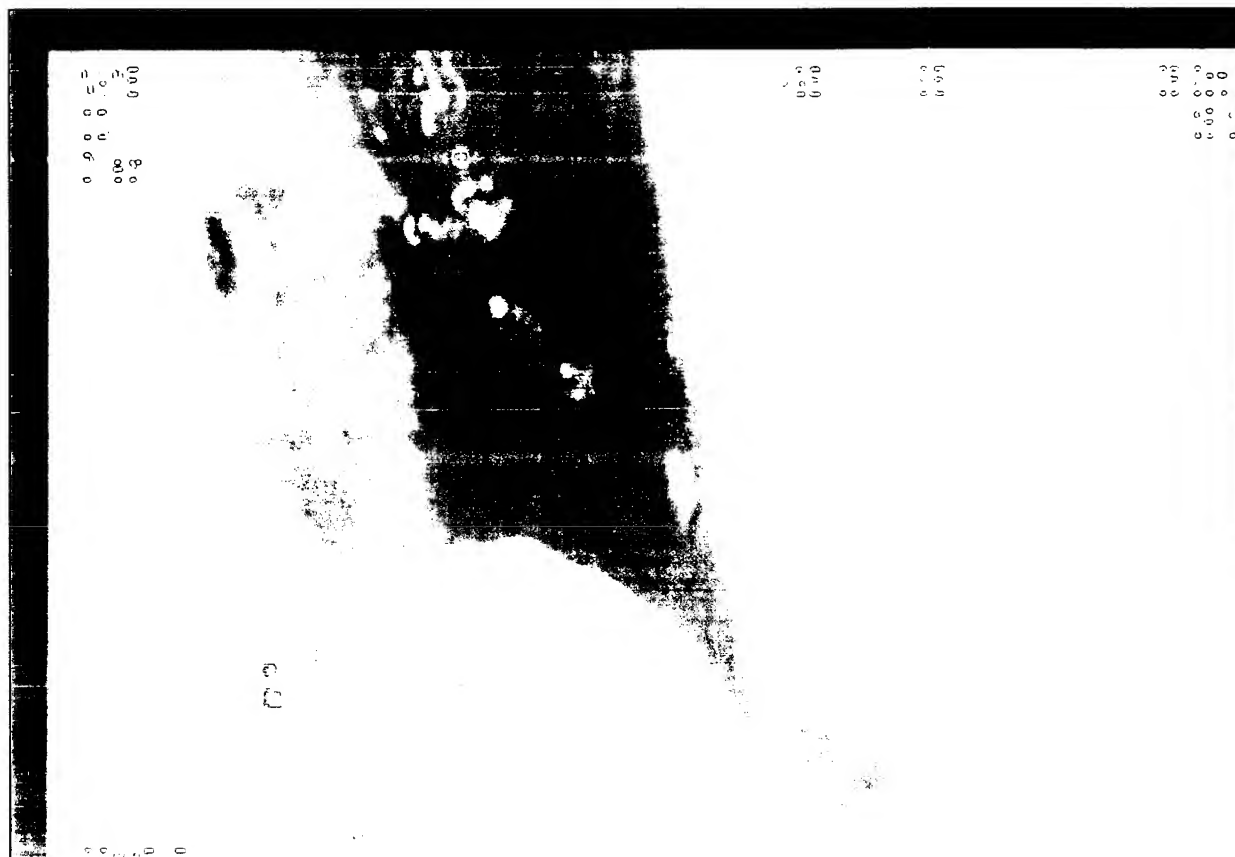


Figure 17. Photograph of bowel of patient administered PicoPrep™ composition.

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Figure 18. Photograph of bowel of patient administered PicoPrepTM composition.

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Figure 19. Photograph of bowel of patient administered PicoPrepTM composition.

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Figure 20. Photograph of bowel of patient administered PicoPrep™ composition prepared in a solution containing a degradable sugar.

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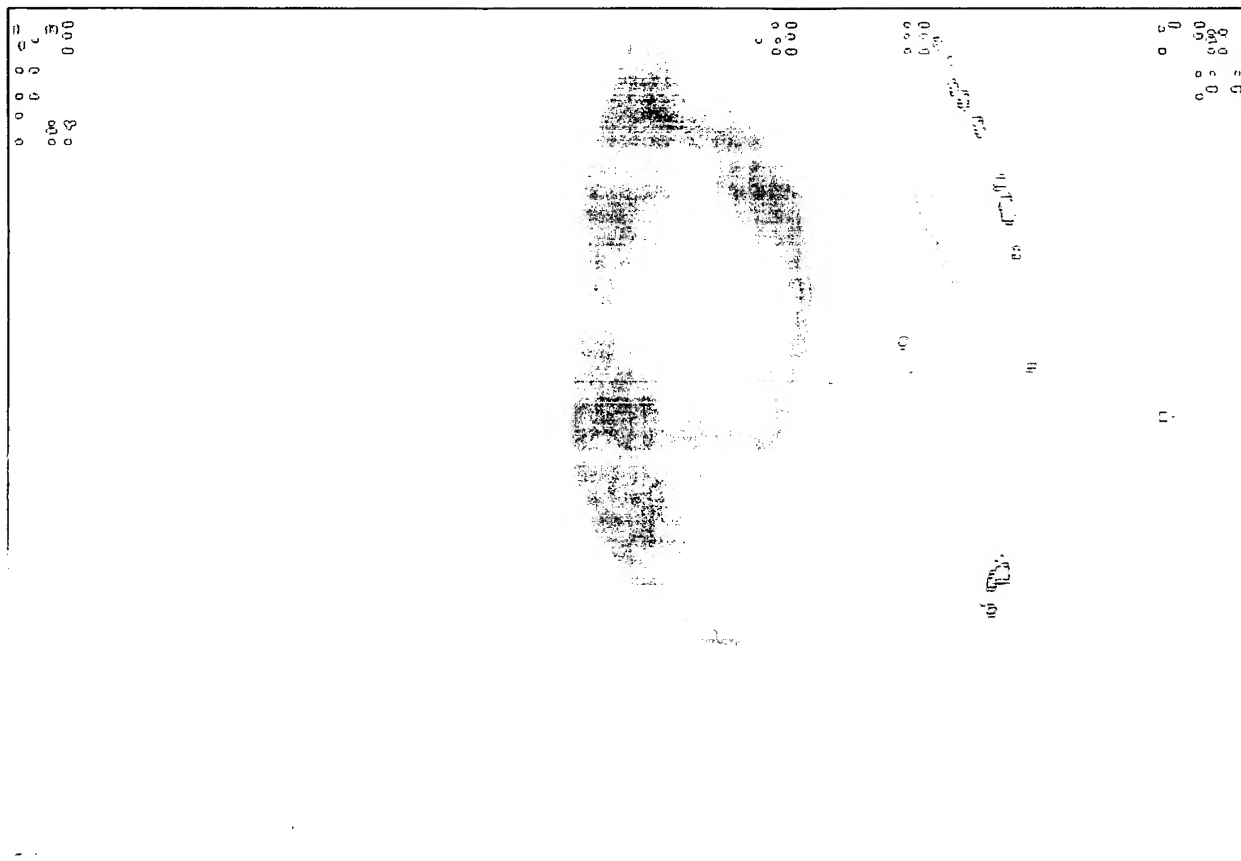


Figure 21. Photograph of bowel of patient administered PicoPrep™ composition prepared in a solution containing a degradable sugar.

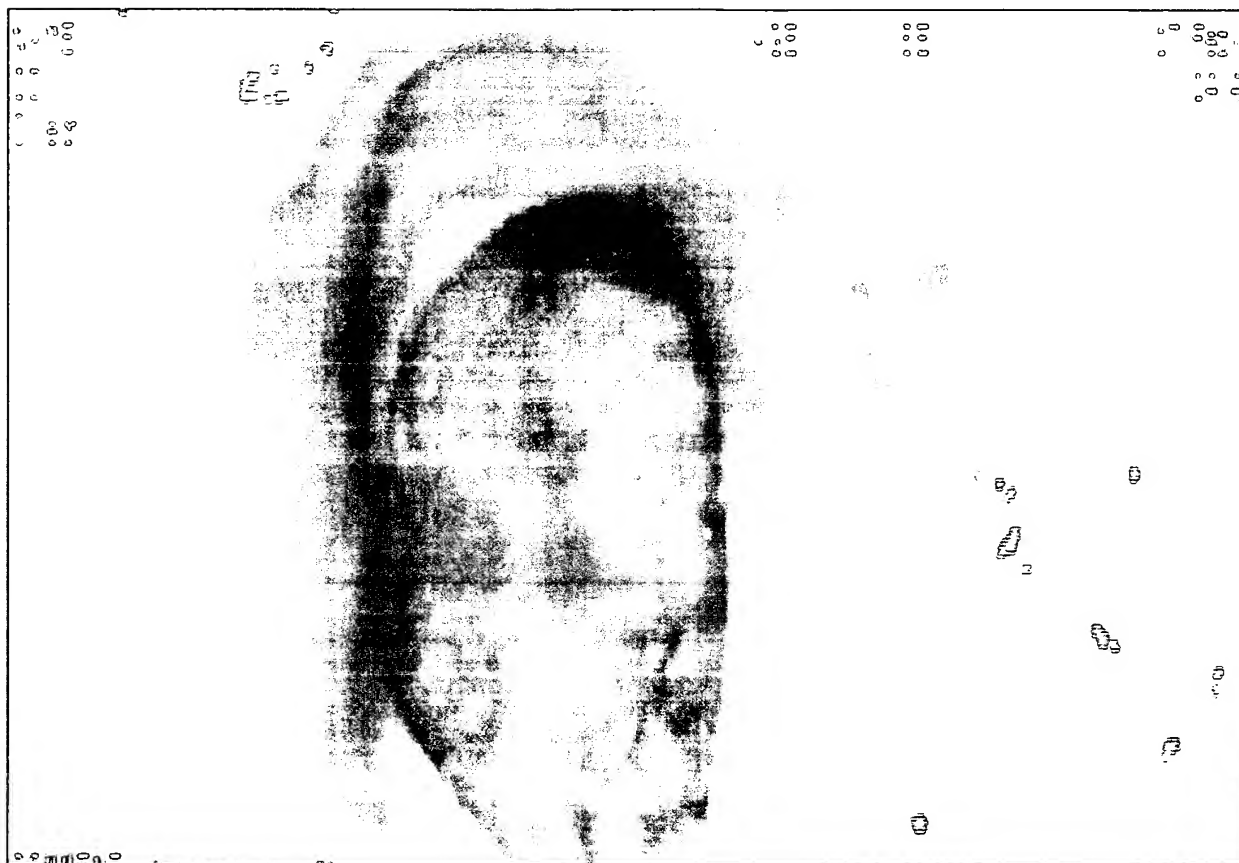


Figure 22. Photograph of bowel of patient administered PicoPrep™ composition prepared in a solution containing a degradable sugar.

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Figure 23. Photograph of bowel of patient administered PicoPrepTM composition prepared in a solution containing a degradable sugar.

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Figure 24. Photograph of bowel of patient administered PicoPrep™ composition prepared in a solution containing a degradable sugar.

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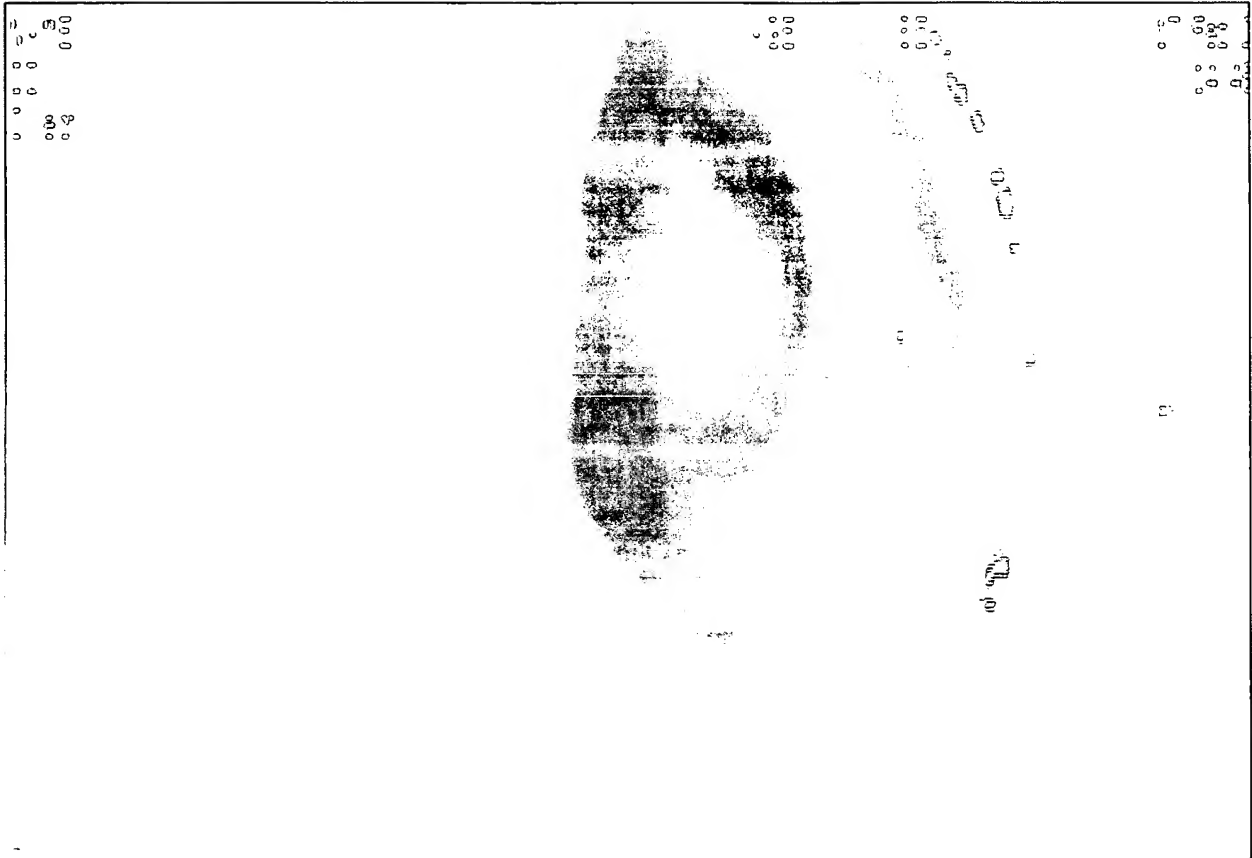


Figure 25. Photograph of bowel of patient administered PicoPrep™ composition prepared in a solution containing a degradable sugar.

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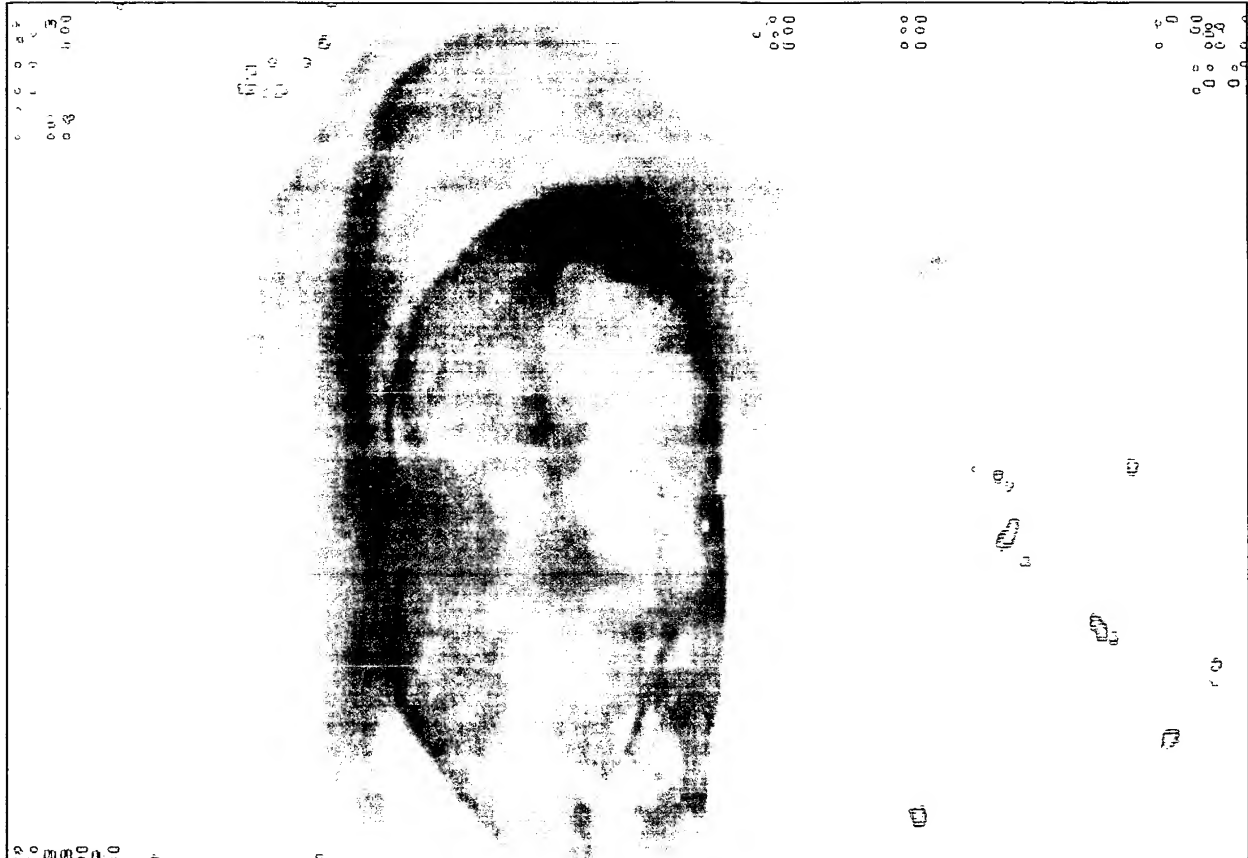


Figure 26. Photograph of bowel of patient administered PicoPrep™ composition prepared in a solution containing a degradable sugar.

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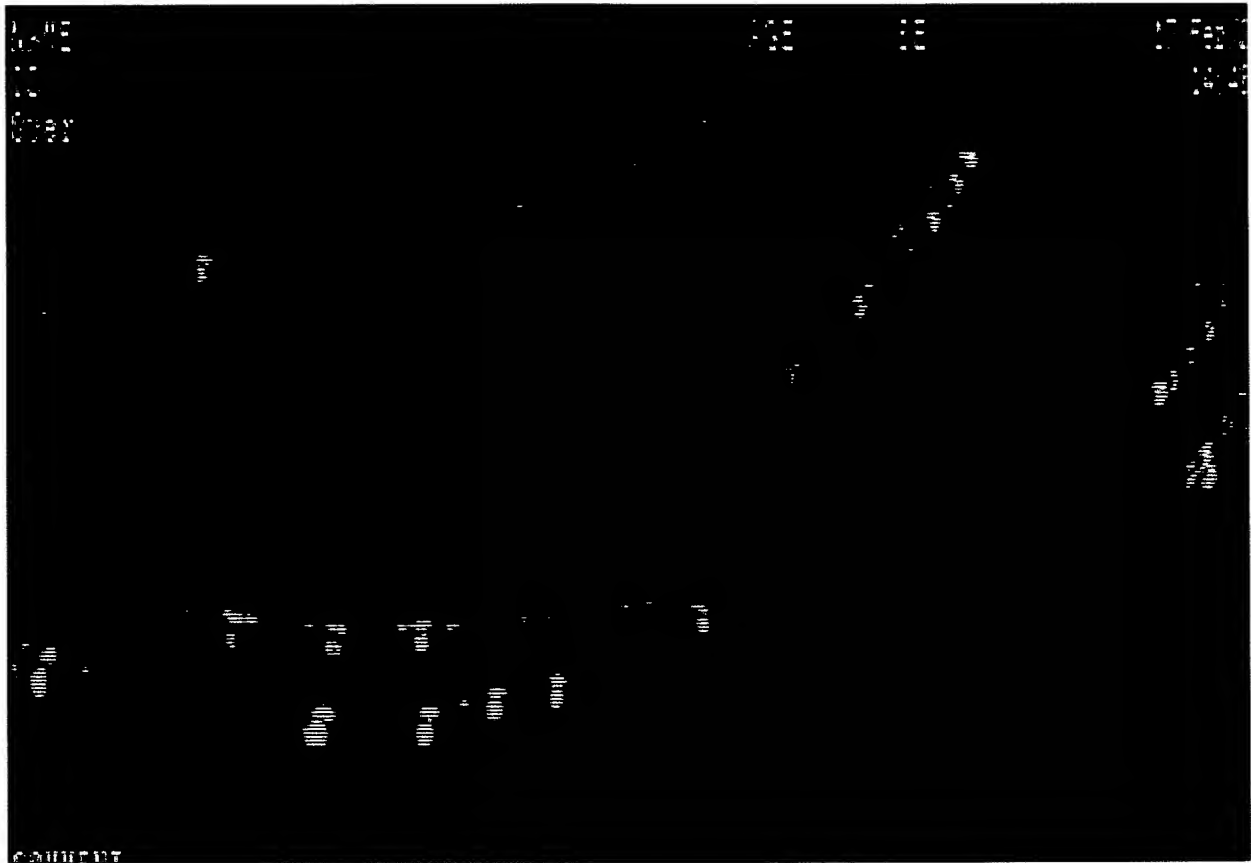


Figure 27. Photograph of bowel of patient administered PicoPrep™ composition prepared in a solution containing a degradable sugar.

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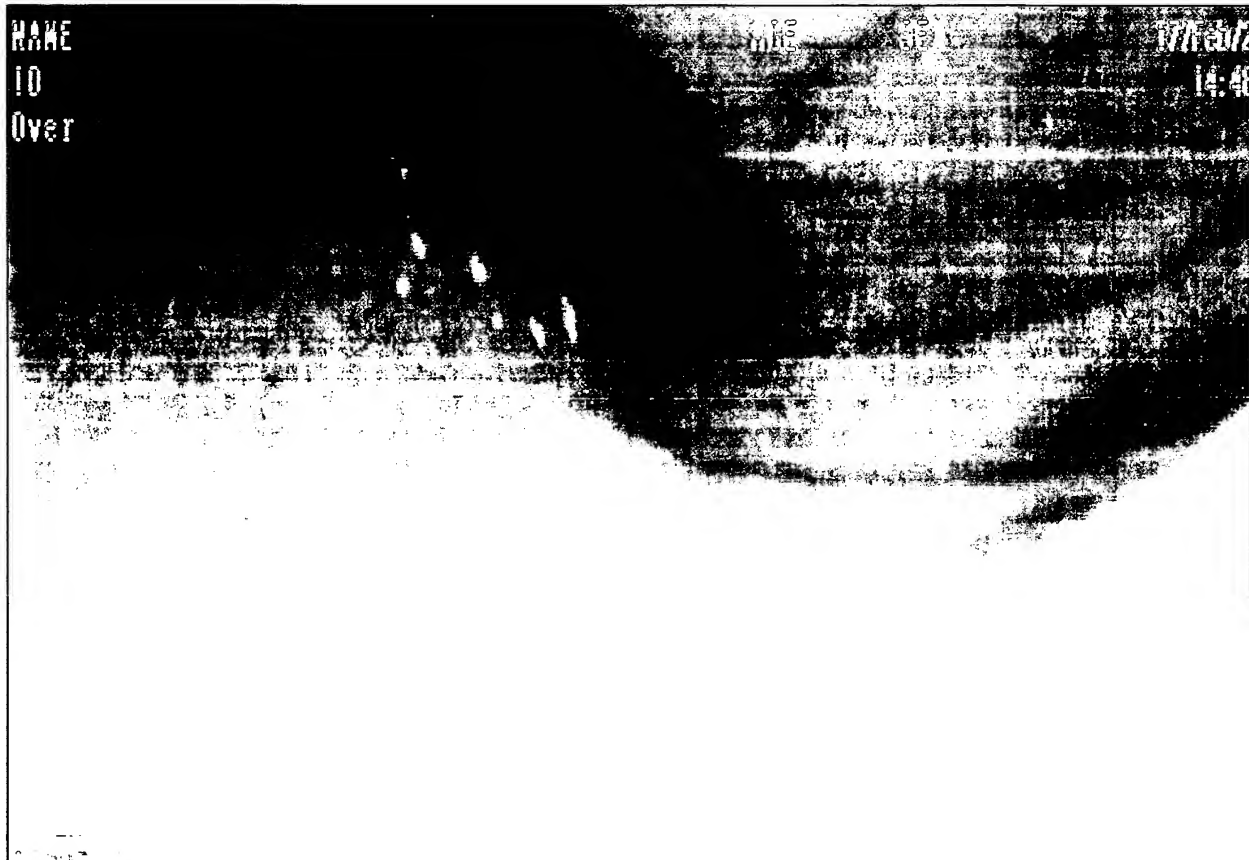


Figure 28. Photograph of bowel of patient administered PicoPrep™ composition prepared in a solution containing a degradable sugar.